

**BIOGRAPHICAL SKETCH**

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NAME: Pertsemlidis, Alexander

POSITION TITLE: Associate Professor of Pediatrics and Cellular & Structural Biology

eRA COMMONS USER NAME (credential, e.g., agency login): aperts

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Princeton University, Princeton, NJ	AB	06/1987	Medieval History
The University of Michigan, Ann Arbor, MI	MS	05/1988	Cell & Molecular Biology
The University of California, Berkeley, CA	PhD	06/1995	Biophysics
UT Southwestern Medical Center, Dallas, TX	postdoctoral	06/1999	Biochemistry
UT Southwestern Medical Center, Dallas, TX	postdoctoral	12/2000	Statistical Genetics

**A. Personal Statement**

I integrate computational biology, cancer biology and genetics to study the pathogenesis of lung cancer and neuroblastoma, with the goal of identifying transcripts (either coding genes or non-coding RNAs) that: (1) are markers of specific subtypes (small cell versus non-small cell lung cancer or high-risk versus low-risk neuroblastoma), (2) are associated with specific cellular responses, and (3) can be manipulated to modulate cell viability or drug response. These investigations are based on more than 20 years of experience in: (a) RNA isolation from cell lines and both frozen and FFPE tissues, (b) expression profiling using Agilent, Illumina and Exiqon microarrays, TaqMan qRT-PCR assays and next-generation sequencing (NGS), (c) design and implementation of analysis pipelines for large datasets, including whole exome and whole genome DNA sequencing and RNA expression profiling, (d) deriving miRNA, lncRNA and mRNA expression signatures and calculating over-representation of microRNA target sites in sets of differentially expressed genes, (e) prediction of interactions between miRNAs, lncRNAs and mRNAs, using both publicly available methods and those that I have developed, and (f) transient or stable manipulation of intracellular levels of transcripts, either individually or by high-throughput screen. I have identified promising candidate biomarkers, therapeutic targets or therapeutic agents, resulting in funding support from the NIH, NSF and DoD, and multiple peer-reviewed publications.

Since 2012, I have served as co-leader of the Cancer Biology Track in the IMGP, and now also serve as the Director for the Cancer Biology Discipline in the new Integrated Biomedical Sciences Program and co-Director for a summer undergraduate research program. I also serve on several committees that focus on graduate student recruitment and curriculum, institutional research strategy, institutional and system-wide computing resources. I teach in and co-direct Functional Genomics Data Analysis (CSBL 6095), and lecture in other graduate school courses including Cancer Biology Core 2 (CSBL 6069), Genomics (CSBL 5024) and the required Fundamentals of Biomedical Sciences course for first-year graduate students (IBMS 5000). Overall, I have supervised 19 graduate students in rotations, 1 postdoctoral fellow (now faculty at Texas State University), 8 undergraduates for summer internships, 1 medical student and 5 high school students. I have participated in dissertation committees for 18 students and mentored 5 graduate students for their dissertation research.

**B. Positions and Honors****Positions and Employment**

2001-2003 *Research Assistant Professor*, Division of Cardiology, UT Southwestern Medical Center, Dallas

2003-2011 *Assistant Professor*, Department of Internal Medicine and the Eugene McDermott Center for Human Growth and Development, UT Southwestern Medical Center, Dallas

- 2011- Associate Professor, Departments of Pediatrics and Cellular and Structural Biology, Greehey Children's Cancer Research Institute, UT Health Science Center, San Antonio
- 2012- Co-Leader, Cancer Biology Track, Integrated Multidisciplinary Graduate Program, Graduate School of Basic Sciences, UT Health Science Center, San Antonio
- 2014- Director, Cancer Biology Discipline, Integrated Biomedical Sciences Graduate Program, Graduate School of Basic Sciences, UT Health Science Center, San Antonio

### **Professional Activities**

Reviewer for *Advanced Drug Delivery Reviews*; *Bioinformatics*; *BMC Bioinformatics*; *BMC Cancer*; *BMC Molecular Biology*; *Cancer Medicine*; *Cancers*; *Cell Death & Disease*; *Clinical Cancer Research*; *Epigenomics*; *Frontiers*; *Fungal Genetics and Biology*; *Gene Therapy*; *Genes, Chromosomes & Cancer*; *Genome Biology*; *Human Molecular Genetics*; *International Journal of Molecular Sciences*; *Journal of Biological Chemistry*; *Journal of Clinical Investigation*; *Journal of the NCI*; *Journal of Thoracic Oncology*; *Lancet Oncology*; *Lung Cancer*; *Medical Oncology*; *Molecular Cancer*; *Molecules*; *Nature*; *Nucleic Acids Research*; *Oncogene*; *Pharmacology & Therapeutics*; *Physiological Genomics*; *PNAS*; *PLoS ONE*; *Scientific Reports*

Guest Associate Editor, *Frontiers in Non-coding RNA*

Board Member, *Texas Genetics Society*

### **Honors and Awards**

UT Southwestern Medical Center

SPORE Career Development Award, 2004-2005, 2006-2007, 2010-2011

ACS New Investigator Award, 2006-2007

University of California at Berkeley

Faculty Associate, Department of Physics, 1990-1991

Regents' Fellowship, 1991-1992

Outstanding Graduate Student Instructor

Committee on Research Faculty Research Grant, 1994-1995

University of Michigan at Ann Arbor

NSF Honorable Mention, 1987-1988

Thurnau Fellowship, 1987-1988

### **C. Contribution to Science**

My current research program is centered on the study of miRNA regulation of cell viability and drug response in cancer, and is aimed at developing sensitive, non-invasive methods for early detection and novel therapeutic agents targeting specific cancer subtypes.

1. In early work, I identified three microRNAs – miR-93, miR-98 and miR-197 – that translationally repress a key tumor suppressor located in the 3p21.3 region where homozygous deletions, loss of heterozygosity and expressional deficiencies are frequently found in human cancers. Inhibiting one or more of these miRNAs is potentially an effective way to abrogate the endogenous repression of Fus1 observed in NSCLC, opening the door to a new therapeutic approach based on combining existing FUS1-expressing nanoparticle approaches with miRNA inhibitors. In more recent work, I showed that miR-93 functions as a potent repressor of DAB2, which also functions as a tumor suppressor gene in lung cancer, with tumor expression levels significantly correlated with poor patient survival. Using *in vitro* and *in vivo* approaches, I demonstrated that miR-93 over-expression promotes lung cancer cell growth, and that its oncogenic function is primarily mediated by down-regulating DAB2 expression. Clinical data further indicated that high tumor levels of miR-93 are correlated with poor survival of lung cancer patients. Together with my original study on miR-93, and studies showing that miR-93 also activates PI3K/Akt signaling through repression of TGFBR2, this further suggests therapeutic value in reducing miR-93 expression in tumor cells.
  - a. Du L, Schageman JJ, Subauste MC, Saber B, Hammond SM, Prudkin L, Wistuba I, Ji L, Roth JA, Minna JD, Pertsemlidis A. miR-93, miR-98, and miR-197 regulate expression of tumor suppressor gene FUS1. *Mol Cancer Res* 2009;7:1234-1243. PMCID: 2741087.
  - b. Du L, Zhao Z, Ma X, Hsiao TH, Chen Y, Young E, Suraokar M, Wistuba I, Minna JD, Pertsemlidis A. miR-93-directed downregulation of DAB2 defines a novel oncogenic pathway in lung cancer. *Oncogene* 2014;33:4307-4315. PMCID: PMC4281941.

2. I developed computational strategies for identifying novel miRNAs and miRNA-like small RNAs and for predicting likely targets of microRNA regulation. The algorithm to identify canonical targets in 3'UTRs has been used in all of our studies. In collaboration with David Corey, I was the first to show that endogenously expressed small RNAs could modulate gene expression by interacting with gene promoters. In collaboration with Yi Liu, I identified several new classes of small RNAs in *Neurospora crassa*, including miRNA-like RNAs (miRNA) and Dicer-independent siRNAs (disiRNAs), revealing several novel small RNA biogenesis pathways. This was the first application of miRNA target prediction methods to fungi, and indicates that miRNAs in *Neurospora*, like their animal and plant miRNA cousins, may induce silencing of their targets mainly by translational inhibition.
  - a. Younger ST, Pertsemlidis A, Corey DR. Predicting potential miRNA target sites within gene promoters. *Bioorg Med Chem Lett* 2009;19:3791-3794. PMID: 2709707.
  - b. Lee HC, Li L, Gu W, Xue Z, Crosthwaite SK, Pertsemlidis A, Lewis ZA, Freitag M, Selker EU, Mello CC, Liu Y. Diverse pathways generate microRNA-like RNAs and Dicer-independent small interfering RNAs in fungi. *Mol Cell* 2010;38:803-814. PMID: PMC2902691.
3. To understand why SCLC is more aggressive than NSCLC, I compared miRNA expression of SCLC cell lines to that of NSCLC cell lines and normal immortalized human bronchial epithelial cells (HBECs). I identified multiple miRNA markers capable of distinguishing SCLC from NSCLC and normal lung epithelial cells and found that miRNA expression typically shows a trend from HBECs to NSCLC cells to SCLC cells, suggesting that increased dysregulation of miRNA expression might be involved in the progression of lung tumors toward a more malignant subtype. In related work with Jon Kurie, we focused on metastatic capacity in a syngeneic tumor model. We found that K-ras and p53 mutations were not sufficient to confer metastatic capacity, and that a single miRNA cluster (miR-200) regulated the capacity of tumor cells to transit reversibly between epithelial and mesenchymal states. Forced expression of the miR-200b cluster reprogrammed cells, locking them in an epithelial state, abrogating their metastatic capacity in syngeneic mice, and conferring transcriptional features that resembled those of metastasis-incompetent cells, supporting a central role for the miR-200 family in metastasis. In complementary work, we showed that miR-34a is a potent tumor suppressor in a *Kras/Trp53*-driven lung adenocarcinoma model, with the miR-200 family down-regulating ZEB1, and ZEB1 down-regulating miR-34, driving pro-metastatic actin cytoskeletal remodeling and supporting the application of both miR-200 and miR-34 as a therapeutic agent.
  - a. Gibbons DL, Lin W, Creighton CJ, Rizvi ZH, Gregory PA, Goodall GJ, Thilaganathan N, Du L, Zhang Y, Pertsemlidis A, Kurie JM. Contextual extracellular cues promote tumor cell EMT and metastasis by regulating miR-200 family expression. *Genes Dev* 2009;23:2140-2151. PMID: PMC2751985.
  - b. Du L, Schageman JJ, Irnov, Girard L, Hammond SM, Minna JD, Gazdar AF, Pertsemlidis A. MicroRNA expression distinguishes SCLC from NSCLC lung tumor cells and suggests a possible pathological relationship between SCLCs and NSCLCs. *J Exp Clin Cancer Res* 2010;29:75. PMID: 2907339.
  - c. Ahn YH, Gibbons DL, Chakravarti D, Creighton CJ, Rizvi ZH, Adams HP, Pertsemlidis A, Gregory PA, Wright JA, Goodall GJ, Flores ER, Kurie JM. ZEB1 drives prometastatic actin cytoskeletal remodeling by downregulating miR-34a expression. *J Clin Invest* 2012;122:3170-3183. PMID: PMC3428095.
4. In recent work, I have combined a high-throughput screening platform with a library of chemically synthesized mimics and inhibitors for all known human miRNAs, an unbiased and comprehensive approach to identify those that reduce cancer cell viability alone or in the presence of otherwise sub-lethal concentrations of chemotherapeutic agents. By screening three lung cancer cell lines with different genetic backgrounds, I identified miRNA mimics and inhibitors that potentially have a universal cytotoxic effect on lung cancer and neuroblastoma cells and several that sensitize cells to paclitaxel treatment. I demonstrated that inhibitors of miR-133a/b and miR-361-3p decrease cell survival by activating apoptotic pathways and inducing cell cycle arrest and miR-337 as selectively sensitizing NSCLC cells to microtubule-targeting agents, with no effect on cell viability in the absence of drug. This work demonstrates that specific miRNA mimics and inhibitors regulate cell survival and drug response and lay the foundation for defining their mechanisms of action and translating the findings into clinical applications.
  - a. Du L, Subauste MC, DeSevo C, Zhao Z, Baker M, Borkowski R, Schageman JJ, Greer R, Yang CR, Suraokar M, Wistuba, II, Gazdar AF, Minna JD, Pertsemlidis A. miR-337-3p and its targets STAT3 and RAP1A modulate taxane sensitivity in non-small cell lung cancers. *PLoS One* 2012;7:e39167. PMID: PMC3377607.

- b. Du L, Borkowski R, Zhao Z, Ma X, Yu X, Xie XJ, Pertsemlidis A. A high-throughput screen identifies miRNA inhibitors regulating lung cancer cell survival and response to paclitaxel. *RNA Biol* 2013;10:1700-1713. PMCID: PMC3907480.
- c. Borkowski R, Du L, Zhao Z, McMillan E, Kostı AK, Yang CR, Suraokar M, Wistuba II, Gazdar AF, Minna JD, White MA, Pertsemlidis A. Genetic mutation of p53 and suppression of the miR-17~92 cluster are synthetic lethal in non-small cell lung cancer due to upregulation of vitamin D signaling. *Cancer Research*, *Cancer Research* 2015;75(4):666-75. PMID: 25519225.
- d. Zhao Z, Ma X, Sung D, Li M, Kostı A, Lin G, Chen Y, Pertsemlidis A, Hsiao TH, Du L. microRNA-449a functions as a tumor suppressor in neuroblastoma through inducing cell differentiation and cell cycle arrest. *RNA Biology* 2015;12(5):538-54.
- e. Zhao Z, Ma X, Shelton SD, Sung DC, Li M, Hernandez D, Zhang M, Losiewicz MD, Chen Y, Pertsemlidis A, Yu X, Liu Y, Du L. A combined gene expression and functional study reveals the crosstalk between N-Myc and differentiation-inducing microRNAs in neuroblastoma cells. *Oncotarget* 2016;7(48):79372-79387.

#### **Complete List of Published Work in MyBibliography:**

<http://www.ncbi.nlm.nih.gov/sites/myncbi/1J9S8stY80652/bibliography/40303034/public/?sort=date&direction=ascending>

#### **D. Research Support**

##### **Active**

(A. Pertsemlidis)

07/01/16-06/30/17

##### **bioAffinity, Inc**

Title: Developing a simple, non-invasive fluorescence-based assay for early lung cancer detection

Goal: To develop an automated early lung cancer detection assay using microscopy and flow cytometry-based technology.

Role: PI

(A. Pertsemlidis)

01/01/16-12/31/17

##### **William and Ella Owens Medical Research Foundation**

Title: Identifying microRNA biomarkers by tissue of origin

Goal: To distinguish tumor from host miRNAs by using a protozoan enzyme, uracil phosphoribosyltransferase (UPRT), to biosynthetically label newly synthesized miRNAs.

Role: PI

(S. Kerwin)

12/01/15-11/30/17

##### **William and Ella Owens Medical Research Foundation**

Title: Hypoxia-derived treatment for advanced lung cancer

Goal: To identify the molecular mechanisms of action of roperol in lung cancer cell lines, design and synthesize analogs and pro-drugs to improve its biological properties, and evaluate analogs to identify potential lead clinical candidate(s).

Role: Co-Investigator

P30 AG013319-22S1 (B. Nicholson, A. Pertsemlidis)

01/01/17-12/31/17

##### **National Institute on Aging/San Antonio Nathan Shock Center**

Title: microRNA expression and dissemination in the progression of Alzheimer's Disease

Goal: To test the hypothesis that inter-cellular communication between glial cells and neurons, specifically mediated by transfer of miRNAs through gap junctions, contributes to the propagation of AD pathology through activation of gamma secretase and APP cleavage.

Role: PI

Pilot Award (Pertsemlidis)

12/01/14-11/30/17

##### **Institute for Integration of Medicine and Science/CTSA**

Title: Elucidating how chromosome 21 protects against neuroblastoma occurrence.

Goal: To evaluate the effect of chr 21 trisomy on tumor cell growth rate in a neuroblastoma cell line model established from isogenic chr 21 disomy/trisomy iPS cells.

Role: PI

**CPRIT (Cancer Prevention and Research Institute of Texas)**

Title: UTHSCSA Cancer Research Training Program

Goal: To train individuals in all aspects of cancer research so that they will have an appreciation of the basic science, translational and clinical areas of research. To accomplish this, we have developed a training program that spans pre- and postdoctoral as well as undergraduate education.

Role: Co-PI and Deputy Director

**Completed**

SBIR R43 CA165450 (A. Bader, miRNA Therapeutics; A. Pertsemlidis, UTHSCSA)

06/01/12-05/01/16

**NIH/NCI**

Title: Therapeutic miRNAs in combination with conventional chemotherapy

Goal: To identify a miRNA/chemo combination with improved efficacy for further clinical development. In Aim 1, miRNA/chemo combinations will be evaluated using cancer cells that are either sensitive or resistant to the individual chemotherapy to identify those that are more effective than chemo alone. In Aim 2, the 1-2 most effective miRNA/chemo combos will be evaluated in animal models.

Role: Co-PI

CBET 1105524 (L. Bleris, UTD; A. Pertsemlidis, UTHSCSA)

09/01/11-08/31/15

**NSF**

Title: Detecting Cancer at the Single-Cell Level Using Endogenous Signal Biomolecular Sensors

Goal: To design, test, and optimize molecular biosensors that are sensitive and specific for combinations of endogenous miRNAs, and construct sensors for colon, hematologic, lung, and pancreatic cell lines.

Role: Co-PI

(Pertsemlidis, Du)

07/01/14-06/30/15

**Helen Freeborn Kerr Charitable Foundation**

Title: What drives regression in neuroblastoma? Clues from Chromosome 21.

Goal: To identify genes that are over-expressed in cells containing three copies of chromosome 21 relative to those only containing two, and in low-risk (stage 4S) relative to high-risk (stage 4) neuroblastoma patients.

Role: PI

PR121532 (L. Du)

09/01/13-08/31/15

**Department of Defense**

Title: Identifying microRNAs that regulate neuroblastoma cell differentiation

Goal: To comprehensively identify neuroblastoma differentiation-inducing and -repressing microRNAs in a high-throughput manner by combining a microRNA mimic library with a high-content screening approach.

Role: Co-Investigator

R01 CA129632 (A. Pertsemlidis)

09/25/07-07/31/13

**NIH/NCI**

Title: microRNA regulation of drug sensitivity in non-small cell lung cancer

Goal: To (1) identify microRNAs that regulate drug response in NSCLC, (2) investigate the functional effects of altering the miRNAs, and (3) identify the target genes of miRNAs that mediate their effects.

Role: PI

## Pertsemlidis Lab Research

Our research program is driven by several core beliefs: (1) We believe that RNA is much more important than the central dogma of molecular biology implies; (2) We believe that adult and pediatric cancers are mutually informative and that we learn from studying one will tell us something useful about the other; and (3) We believe that non-coding RNAs, including short non-coding RNAs like microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), can be used both as therapeutic agents and as probes of therapeutically relevant pathways. Importantly, all of our projects integrate *in silico*, *in vitro* and *in vivo* approaches.

The two types of cancer that we have chosen to study, lung cancer and neuroblastoma, represent very different cancers: The two localize to different organs; lung cancer is almost exclusively a disease of adults, while neuroblastoma occurs only in children. But there are also surprising similarities between the two, and both are more complicated than labeling either as single, homogeneous disease would suggest.

**Lung cancer** is divided into two major groups. 15% of bronchogenic carcinomas are small cell lung carcinomas (SCLC). Untreated SCLC has the most aggressive clinical course of any type of pulmonary tumor, with median survival of only 2-4 months from diagnosis. SCLC is typically diagnosed only when the disease has already metastasized, beyond the point at which surgical or radio/chemotherapeutic intervention is likely to be of benefit. The other 85% of bronchogenic carcinomas are non-small cell lung carcinomas (NSCLC), which is made up of several histological subtypes, including adenocarcinoma, squamous cell carcinoma and large cell carcinoma. NSCLC progresses relatively slowly, and is characterized by significant heterogeneity in its response to treatment. This dichotomy between NSCLC and SCLC raises interesting questions: **(1) Are specific genes or non-coding RNAs differentially expressed between states or between extremes of a phenotype within a state, like drug response? (2) Can a phenotype like drug response be changed by altering intracellular levels of a gene or non-coding RNA? (3) Can one subtype be turned into the other? Is SCLC a state that can be turned off?** A major molecular difference between NSCLC and SCLC is the expression of a neuroendocrine program in the latter, including markers such as CHGA, SYP and NCAM. Interestingly, some SCLC has lost its neuroendocrine program, and some NSCLC has gained a neuroendocrine program.

**Neuroblastoma (NB)** is a tumor that originates from neural crest precursor cells. It is the most common cancer in infants and the most common extracranial solid tumor in children, accounting for 15% of all childhood cancer deaths. The disease is highly heterogeneous, and is stratified into low- and high-risk categories. The overall prognosis for those with high-risk or relapsed disease remains poor despite the standard therapies of surgery, radiation, and chemotherapy. Low-risk neuroblastoma, however, frequently shows spontaneous regression, mainly in tumors with a near triploid number of chromosomes. The dichotomy between low- and high-risk neuroblastoma also raises interesting questions: **(1) What are the molecular differences between low-risk and high-risk NB that lead to spontaneous regression in the former? Is the presence of additional copies of chromosomes in low-risk NB a clue as to the molecular mechanisms underlying regression? (2) Can specific genes or ncRNAs be altered to selectively kill NB cells or improve response to drug?** Interestingly, there are strong similarities between SCLC and NB with respect to the expression of a neuroendocrine program, amplification of Myc-family genes like MYCN, the sites to which both diseases metastasize (bone marrow) and their response to drug, both with respect to initial response (>80%) and the drugs used for treatment.

Our investigations are uncovering novel mechanisms of regulating intracellular signaling pathways — through the identification of ncRNAs that have direct therapeutic applications or through the elucidation of pathways that can be targeted through more traditional pharmacological interventions — and providing novel drug candidates for cancer treatment and novel, non-invasive biomarkers for predicting patient survival and developing personalized therapeutic regimens. These investigations have contributed to our understanding of non-coding RNA roles in cancer pathogenesis. We are extending the work to study how ncRNAs mediate intracellular transport and inter-cellular communication.